UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/258,217	02/26/1999	MARK T. KEATING	2323-127	3509

6449 7590 04/03/2002

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	22

DATE MAILED: 04/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/258,217	Applicant(s) KEATING ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 1-18-02 has been entered. Claims 1, 2, 5, 6, 9 and 10 have been amended. Claims 1-6, 9 and 10 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 6 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making an ELN+/- mouse having increased number of elastic lamellae and ELN-/- mouse having arterial occlusion, does not reasonably provide enablement for making any ELN +/- mouse having various phenotypes other than the disclosed ELN +/- and ELN-/- mice, and a method for screening drug candidates useful for treating SVAS, hypertension or atherosclerosis by inhibition of elastase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 7-18-01 (Paper No. 20). Applicant's arguments filed 1-18-02 have been fully considered but they are not persuasive.

Applicants argue that claim 6 is directed to a method for screening drug candidates which may be useful in treating or preventing atherosclerosis, SVAS or essential hypertension in

humans and for the purpose of narrowing down the number of drug candidates (amendment, page 4). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 7-18-01 (Paper No. 20). There is still no correlation between the inhibition of elastase activity and treating humans with atherosclerosis, SVAS or essential hypertension or preventing atherosclerosis in humans. The rationale of inhibiting elastase activity would reduce the metabolism of elastin by elastase fails to provide sufficient correlation between the inhibition of elastase activity and treating humans with atherosclerosis, SVAS or essential hypertension or preventing atherosclerosis in humans. Thus, claim 6 remain rejected under 35 U.S.C. 112 first paragraph.

3. Claims 1, 2, 5, 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making an ELN+/- mouse having increased number of elastic lamellae and ELN-/- mouse having arterial occlusion, does not reasonably provide enablement for making any ELN +/- mouse having the phenotype of arterial occlusion or any ELN -/- mouse having the phenotype of increased number of elastic lamellae. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants' amendment filed 1-18-02 necessitates this new ground of rejection.

Claims 1 and 2 are directed to a mouse having only one functional elastin gene and with no functional elastin gene, respectively, wherein said mouse has an increased number of elastic

lamellae and arterial occlusion. Claim 5 is directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis, or preventing atherosclerosis by using an ELN +/- mouse or human having only one functional elastin gene, wherein said drug candidates inhibit occlusion of arteries. Claims 9 and 10 are directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using ELN +/- mouse or human or ELN +/- cells having only one functional elastin gene and by measuring the synthesis of elastin mRNA or synthesis of elastin.

The specification discloses the generation of ELN +/- mice having 47% decrease in ELN mRNA and 50% thinner in elastic lamellae as compared to ELN +/+ mice, and ELN-/- mice having arterial occlusion and the ELN-/- mice were dead by P4.5. The specification fails to provide an enabling disclosure for the preparation of any ELN +/- mouse having the phenotype of arterial occlusion or any ELN -/- mouse having the phenotype of increased number of elastic lamellae. No teachings are present within the specification in regard to how one would have prepared any ELN +/- mouse having the phenotype of arterial occlusion or any ELN -/- mouse having the phenotype of increased number of elastic lamellae.

The state of the art in the field of transgenics at the time of the invention was unpredictable. Transgene expression and phenotypic/physiological results of such expression is not always accurately predictable and the phenotype of a transgenic knockout organism is unpredictable. Houdebine, 1994 (U2) points out that transgene expression in transgenic animal is heavily dependent on its site of integration in the host genome rather than on the number of

copies, the site of integration of a gene is unpredictable and thus the expression of a transgene in a given animal is unpredictable when the DNA is microinjected into the pronuclei by the conventional method (e.g. p. 277).

Wu et al., 1997 (Methods in Gene Biotechnology, CRC Press, Boca Raton, p. 339-365) pointed out that the approach of using ES cells carrying a single-copy mutation of a specific gene to generate knockout transgenic animal is time-consuming and costly to obtain homozygous or double-knockout mice, and another major concern is the potentially lethal effect of the targeted gene. In some cases, gene knockout results in early death of embryos and young animals, or morphologically and functionally abnormal offsprings such as blind and/or handicapped animals (e.g. p. 340). Anders et al. (2000, Experimental Nephrology, Vol. 8, No. 4-5, pp. 181-193) reports that "the phenotype of many disease models is rather strain specific and depends on the genetically determined immune response after a certain stimulus...The problem of an undefined genetic background in transgenes also includes the lack of adequate controls. Because of marked polymorphism in the genetic background of many laboratory mouse strains, it cannot be concluded that the null mutation is the only cause for a phenotypical change" (e.g. page 182) and "As the genetic background is of such importance for transgenic studies, reproducible models of renal disease with a well-defined genetic background are essential" (e.g. p. 183). In view of the unpredictability of the resulting phenotypes of the ELN transgenic knockout mice, the importance of the genetic background of the mice for transgenic studies, and various factors that can influence the resulting transgenic mice, one skilled in the art at the time of the invention

would not know how to make and use the ELN +/- mouse having the phenotype of arterial occlusion or the ELN -/- mouse having the phenotype of increased number of elastic lamellae and would have to engage in undue experimentation to practice over the full scope of the invention claimed.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to have made and used the full scope of the claimed inventions. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 3-4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sechler et al., 1995 (U) in view of Morris, 1998 (Current Opinion in Cardiology, Vol. 13 (3), p. 214-219) and Wydner et al., 1994 (X2) and is repeated for the reasons set forth in the preceding Official action mailed 7-18-01 (Paper No. 20). Applicant's arguments filed 1-18-02 have been fully considered but they are not persuasive.

Applicants argue that reference Morris is not a prior art but fail to file an appropriate declaration to overcome Morris as a prior art. Therefore, the cited reference Morris remains a prior art and the 35 U.S.C. 103(a) rejection stands.

Applicants argue that the cited references teach using mutated mouse elastin gene where the mutated mouse elastin incorporates with normal mouse elastin in elastin matrix but fail to teach knockout one or both the elastin gene expression which results in deficient in elastin. Applicants further argue that there is not motivation to produce mice which are deficient in elastin (amendment, page 5, 6, 7). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 7-18-01 (Paper No. 20). It was well known in the art to produce **knockout** mice having a particular gene expression being **knockout** and are deficient in gene expression of said gene. Further, as discussed in the previous Official action, Morris teaches that "Individuals with Williams syndrome are hemizygous for the elastin gene, owing to a 1 to 2 megabase **deletion** of a portion of the long arm of chromosome 7 that encompasses ELN... Experiments with **elastin knockout** mice will likely yield clues regarding the role of elastin in arterial morphogenesis and the pathogenesis of obstructive vascular disease" (e.g. abstract). The teaching of Morris would provide motivation for one of ordinary skill in the art at the time of the invention to produce ELN +/- or ELN-/- mice deficient in elastin gene expression and mouse cells with no functional elastin gene or with one functional elastin gene and no second elastin gene. Thus, claims 3 and 4 remain rejected under 35 U.S.C. 103(a).

Conclusion

No claims is allowed.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MEP. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER